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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): 13151-2

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on 10 April 2006

Signature: /J. David Ellett/

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Application Number	Filed
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First Named Inventor: LINCOLN, Stephen E.

Art Unit	Examiner
1637	FREDMAN, Jeffrey Norman

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant/inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [X] attorney or agent of record. Registration number 27,875.
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

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NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

- [ ] *Total of _____ forms are submitted.

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Request for Pre-Appeal Brief Conference – Remarks

A.1) In an Office Action dated 12 October 2005 now on appeal, claims 75, 76, 78 through 82 inclusive, 85, 86, 91 through 93 inclusive, 95, 96 through 98 inclusive, 102, 106 through 109 inclusive, and 112 through 115 inclusive were finally rejected under 35 U.S.C. §103(a) as unpatentable over a publication by Kimpton *et al.* in *PCR Methods and Applications*, volume 3, pages 13 through 22 (August 1993) ("the Kimpton *et al.* publication") in view of a publication by Ledwina *et al.* in *Biometrics,* volume 36, pages 160 through 165 (1980) ("the Ledwina *et al.* publication") and further as assertedly motivated in view of a publication by Jeanpierre in the *Annals of Human Genetics*, volume 56, page 325 through 330 (1992) ("the Jeanpierre publication"). (Claim 77 was identified as a pending claim in the Office Action on appeal; however, claim77 was previously cancelled without prejudice in a Reply to a Final Office Action filed 27 January 2005.) As outlined below, the final rejections under 35 U.S.C. §103(a) were unwarranted and should be withdrawn by the pre-appeal brief conference panel for at least the following reasons:

A.2.*i*) Turning first to independent claim 75, as discussed briefly below, none of the Kimpton *et al.* publication, the Ledwina *et al.* publication, and the Jeanpierre publication individually disclosed certain elements of the method of independent claim 75 and moreover the three publications considered singly or in any combination would not have suggested such elements to a person of ordinary skill in the art as of the effective filing date of the subject application. Thus, not even a *prima facie* case of unpatentability for obviousness of claim 75 with respect to the three cited publications was made in the Office Action on appeal.

A.2.*ii*) Specifically, independent claim 75 of the subject application as amended is directed to a method for determining the genotype of a subject at a genetic locus within genetic material obtained from a biological sample from the subject which includes a step, among others, of establishing a distribution set of probability distributions associating hypothetical reaction values with corresponding probabilities for each genotype of interest at the locus. The method of amended claim 75 further includes the steps of reacting the material at the locus to obtain a first reaction value indicative of the presence of a given allele at the locus and applying the first reaction value to each pertinent probability distribution to determine a measure of a conditional probability of each genotype of interest at the locus. The method of claim 75 as amended also includes a step of determining the genotype based on data from the step of applying the first reaction value to each pertinent probability distribution.

A.2.*iii*) In the Office Action of 12 October 2005 at page 5 it was conceded – correctly, it is submitted – that the Kimpton *et al.* publication did not disclose "establish[ing] a distribution set of probability distributions" and did not disclose applying a "reaction value of the distributions to determine a measure of a conditional probability of each genotype of interest at [a] locus." However, contrary to the assertions in the Office Action, neither the Ledwina *et al.* publication nor the Jeanpierre publication would have suggested, let alone disclosed, any probability distribution which associated hypothetical reaction values with corresponding probabilities for each genotype of interest at the locus, as discussed briefly below. Consequently, the combination of the Kimpton *et al.* publication, the Ledwina *et al.* publication, and the Jeanpierre publication proposed in the Office Action on appeal does not constitute even a *prima facie* case of obviousness with respect to the method of claim 75.

A.2.*iv.1*) Turning now to the Ledwina *et al.* publication, as explained in detail on pages 24 through 30 of a Reply to an Office Action filed on 22 August 2005 with respect to the subject application, the Ledwina *et al.* publication addressed a problem in population genetics, in contrast to the problem of determination of the genotype of an individual subject, to which claim 75 relates. The assertion on page 5 of the Office Action on appeal that "Ledwina teaches a method in which genotypes can be determined" was simply incorrect and mischaracterized the Ledwina *et al.* publication in a way which suggested that the publication might have been directly relevant to the method of claim 75 of determining the genotype of a subject, when in fact the publication was not.

A.2.*iv.2*) The problem in population genetics addressed by the Ledwina *et al.* publication concerned formulating mathematically a statistically-rigorous test for accepting or rejecting the hypothesis that a particular population of individuals exhibited a certain set of algebraic relations between, on the one hand, the frequencies of genotypes over the population with respect to a genetic locus and, on the other hand, the frequencies of the component alleles of those genotypes, which set of relations defined a population-genetics state known as "Hardy-Weinberg equilibrium." The statistical test for accepting or rejecting the hypothesis that the population exhibited Hardy-Weinberg equilibrium was based on data separately enumerating the aggregate number of individuals having each different genotype in a sample of N individuals randomly selected from the population. Compiling a set of data enumerating the aggregate number of individuals from a sample having each different genotype requires that the genotype of each individual in the sample be determined. The particular method by which the genotype of an individual may have been determined to obtain data enumerating the aggregate number of individuals from the sample having each different genotype was entirely irrelevant to the mathematical derivation of the statistical test for Hardy-Weinberg equilibrium set out in the Ledwina *et al.* publication and no such method was specified, recommended, or suggested in the publication. In particular, no mention was made in the Ledwina *et al.* publication of obtaining reaction values in connection with any genotyping method.

A.2.*iv.3*) In the course of the derivation of the statistical test for accepting or rejecting the hypothesis that a population exhibited Hardy-Weinberg equilibrium, probability distributions in several different algebraic forms were set out in the Ledwina *et al.* publication – see, for example, equations (1), (2), and (3) of the publication. However, each of the probability distributions in the Ledwina *et al.* publication was a function of and associated probabilities with respect to one or more random vectors denoted **X**, **T**, and **Z** in the publication, each of whose components, in the case of the random vectors **X** and **T**, respectively specified the aggregate number of individuals in a sample of N individuals who had a corresponding one of the possible allele-pair genotypes, denoted A_iA_j, associated with a genetic locus, or, in the case of the vector **Z**, each of whose components respectively specified the aggregate number of copies of a corresponding allele A_k represented among the genotypes A_iA_j respectively associated with the N individuals of the sample. An imaginary thought experiment demonstrates that the probability distributions of the Ledwina *et al.* publication could not in general have been used to determine the genotype of an individual subject, contrary to the assertions in the Office Action on appeal. In particular, the aggregate numbers specified by the components of the random vectors **X**, **T**, and **Z** of the various probability distributions of the Ledwina *et al.* publication would have remained invariant had any pair of individuals in the sample having different genotypes somehow magically swapped genotypes with one another with respect to some locus, and consequently any probabilities from probability distributions that were a function of such

random vectors would have necessarily remained unchanged under such a genotype swap, demonstrating that such probability distributions were useless for determining the respective genotypes of individual subjects in samples with more than one genotype.

A.2.*iv.4*) In contrast, as noted above, claim 75 of the subject application is directed to a method for determining the genotype of a subject which includes the steps, among others, of reacting genetic material obtained from a biological sample from the subject at a locus to produce a reaction value indicative of the presence of a given allele at the locus and applying the reaction value to each pertinent probability distribution in a distribution set of probability distributions associating hypothetical reaction values with corresponding probabilities for each genotype of interest at the locus to determine a measure of a conditional probability of each genotype of interest at the locus. Even the combination of the Kimpton *et al.* publication and the Ledwina *et al.* publication proposed in the Office Action on appeal would not have suggested the method of claim 75 to a person of ordinary skill in the art as of the effective filing date of the subject application, if for no other reason than that neither publication disclosed or would have suggested any probability distribution associating reaction values with corresponding probabilities. Applying our imaginary thought experiment discussed above to the method of claim 75, swapping the genotypes of two individuals prior to carrying out the method with respect to each individual would result in the respective reaction values obtained from the two individuals also being swapped, so that the measures of conditional probability for each genotype determined for each individual subject would be particular to that individual subject's genotype and could be used as claimed to determine the subject's genotype, unlike the swap-invariant probabilities from the probability distributions disclosed in the Ledwina *et al.* publication discussed above.

A.2.*v*) Turning now to the Jeanpierre publication, the Jeanpierre publication disclosed a method for deriving the probability for a genotype of a person who was "unsampled" with respect to the locus of the genotype, which method made use of genotype assignments of family members in the pedigree of the unsampled person. However, particular methods by which the genotypes could be assigned to family members who were sampled in the pedigree of the unsampled person, other than observation of the expression of a particular genetic disease in such family members, were irrelevant to the derivations of the Jeanpierre publication, and none was specified, recommended, or suggested. On page 6 of the Office Action on appeal, it was asserted that the Jeanpierre publication would have motivated "the use of computation of unknown genotypes to analyze the conditional probabilities relative to a distribution of hypothetical reaction values." However, like the Kimpton *et al.* and the Ledwina *et al.* publications, the Jeanpierre publication made no mention of probability distributions associating hypothetical reaction values with corresponding probabilities, conditional or otherwise. The assertion in the Office Action that the Jeanpierre publication would somehow have motivated analysis of distributions of hypothetical reaction values nowhere disclosed in any of the three cited publications constituted an impermissible importation of subject matter from the disclosure of the subject application and represented an improper hindsight recreation of the invention of claim 75.

A.3) It was asserted additionally with respect to motivation on page 6 of the Office Action on appeal that an ordinary practitioner would have been motivated to apply a hypothetical distribution analysis to genotyping by the method of the Kimpton *et al.* publication in order "to more accurately determine the genotype." However, as explained on pages 19 through 21 of the 22 August 2005 Reply, in the genotyping method disclosed in the Kimpton *et al.*

publication, the loci to be analyzed by gel electrophoresis were deliberately selected so as to permit precise and unambiguous allele designation using polyacrylamide gels. It was noted expressly in the third column on page 13 of the Kimpton *et al.* publication that such precise allele designation "eliminate[ed] the need for continuous allele distribution models currently employed with VNTR [variable number tandem repeat] systems." The Kimpton *et al.* publication thus did not merely express a preference for the technique of limiting the loci selected for genotype determination by gel electrophoresis to loci which permitted precise and unambiguous allele designation, but more emphatically would have affirmatively motivated persons of ordinary skill in the art to avoid any attempt to use probability distributions in connection with such a genotype-determination method. A practitioner purporting to use the genotyping method disclosed in the Kimpton *et al.* publication who nonetheless looked for some statistical distribution-analysis method to determine genotypes more accurately, as proposed in the Office Action on appeal, would have been going against the plain disclosure of the Kimpton *et al.* publication read as a whole. See *Bausch & Lomb v. Barnes-Hind/Hydrocurve*, 230 USPQ 416, 420 (Fed. Cir. 1986) *cert. denied.*

A.4) It was asserted on page 6 of the Office Action on appeal that it would have been obvious to one of ordinary skill in the art to modify the genotyping method of the Kimpton *et al.* publication to use a conditional probability method assertedly disclosed in the Ledwina *et al.* publication since both publications used Hardy-Weinberg equilibrium analysis in some way. However, the observation that both publications used some form of Hardy-Weinberg equilibrium analysis is a red herring with respect to the assertion that it would have been obvious to modify the genotyping method of the Kimpton *et al.* publication somehow in view of the disclosure of the Ledwina *et al.* publication, since, as pointed out above, Hardy-Weinberg equilibrium analysis applied only to population genetics, in contrast to the determination of the genotype of an individual subject to which the method of claim 75 is directed. As discussed on pages 24 through 26 and 29 through 30 of the 22 August 2005 Reply, Hardy-Weinberg equilibrium analysis was applied in the Kimpton *et al.* publication to genotype/allele enumeration data from samples of at least 50 individuals randomly selected from each of three different populations: Caucasian, Afro-Caribbean, and Asian. Neither the Kimpton *et al.* publication nor the Ledwina *et al.* publication disclosed or suggested using a test for Hardy-Weinberg equilibrium in connection with the determination of the genotype of an individual subject. As persons of ordinary skill in the art would have appreciated, any test for Hardy-Weinberg equilibrium takes as input genotype-enumeration data for a population sample based on genotype identifications which would have been made independently of the test for Hardy-Weinberg equilibrium by some suitable genotyping method.

A.5) The reasoning set forth above with respect to claim 75 applies on a generally parallel basis to independent claims 96 and 106 of the subject application, as discussed on pages 22 through 24 of the 22 August 2005 Reply, which discussion, for brevity, will not be summarized here. Each of claims 76, 78 through 82 inclusive, 85, 86, 91 through 93 inclusive, 95, 97, 98, 102, 107 through 109 inclusive, and 112 through 115 inclusive is a dependent claim which respectively depends directly or indirectly on one of independent claims 75, 96, and 106 and consequently incorporates the limitations of one of claims 75, 96, and 106 by reference. The reasoning set forth above concerning distinctions between the Kimpton *et al.* publication considered alone or in combination with the Ledwina *et al.* publication or the Jeanpierre publication and the method of any of independent claims 75, 96, and 106 as amended therefore applies with equal force with respect to the dependent claims listed in the preceding sentence. In sum, for the reasons set forth above,

it is submitted that the final rejection under 35 U.S.C. § 103(a) of claims 75, 76, 78 through 82 inclusive, 85, 86, 91 through 93 inclusive, 95, 96 through 98 inclusive, 102, 106 through 109 inclusive, and 112 through 115 inclusive of the subject application as amended as unpatentable over the Kimpton *et al.* publication in view of the Ledwina *et al.* publication and further as assertedly motivated in view of the Jeanpierre publication was unwarranted and should be withdrawn.

B) In the Office Action on appeal, claims 75, 76, 78 through 82 inclusive, 85 through 87 inclusive, 91 through 98 inclusive, 100, 102, and 106 through 115 inclusive were finally rejected under 35 U.S.C. § 103(a) as unpatentable over the Kimpton *et al.* publication in view of the Ledwina *et al.* publication and further as assertedly motivated in view of the Jeanpierre publication, and further in view of published International Patent Application WO 92/15712 to Goelet *et al.* ("the Goelet *et al.* '712 published international application"). For the reasons discussed in the 22 August 2005 Reply on pages 35 and 36, the Goelet *et al.* '712 published international application does not cure the infirmities of the Kimpton *et al.* publication, the Ledwina *et al.* publication, and the Jeanpierre publication, singly or in any combination, as references against the claims of the subject application. Additionally; like each of the Kimpton *et al.*, Ledwina *et al.*, and Jeanpierre publications; the Goelet *et al.* '712 published international application made no mention of probability distributions associating hypothetical reaction values with corresponding probabilities, and thus the combination of the four cited publications proposed in the Office Action on appeal would not have suggested the subject matter of the claims of the subject application to a person of ordinary skill in the art. It is submitted that the final rejection under 35 U.S.C. § 103(a) of claims 75, 76, 78 through 82 inclusive, 85 through 87 inclusive, 91 through 98 inclusive, 100, 102, and 106 through 115 inclusive of the subject application as amended as unpatentable over the Kimpton *et al.* publication in view of the Ledwina *et al.* publication and further as assertedly motivated in view of the Jeanpierre publication, and further in view of the Goelet *et al.* '712 published international application, was unwarranted and should be withdrawn.

C) In the Office Action on appeal, claim 94 was rejected under 35 U.S.C. § 112, second paragraph, with the assertion that the expression "including such amplification by a polymerase chain reaction or a ligase chain reaction" in the expression "assaying for the given allele using genetic bit analysis, allele-specific hybridization, or allele-specific amplification, including such amplification by a polymerase chain reaction or a ligase chain reaction" recited in the claim was vague and indefinite and lacked clear antecedent basis. We submit that the antecedent basis of "including such amplification" in the immediately preceding term "allele-specific amplification," the only prior use of the word "amplification" in the claim, would have been immediately recognized by a person of ordinary skill in the art as a matter of basic English-language sentence construction and that the claim as presently worded is entirely clear and definite. Compare *MercExchange v. eBay*, 74 USPQ2d 1225, 1237 (Fed. Cir. 2005) *cert. granted with respect to a separate issue.* The final rejection of claim 94 under 35 U.S.C. § 112, second paragraph, was without basis and should be withdrawn.

D) Other good and compelling reasons for withdrawing the final rejections in the Office Action on appeal of the claims of the subject application are set forth in the Reply of 22 August 2005, which for brevity will not be summarized here. It is submitted, in conclusion, that the claims of the subject application are allowable over the art of record and fully meet the standards of 35 U.S.C. § 112, second paragraph, and that therefore the Office Action on appeal presents no actual issues for appeal. A decision by the pre-appeal brief conference panel withdrawing the final rejections and allowing the application is therefore earnestly solicited.